이학석사 학위논문

Cu-Catalyzed Enantioselective 1,4-Addition of 1,1-Bis[(pinacolato)boryl]methane

구리 촉매를 이용한
1,1-비스피나콜라토보릴메테인의
입체선택적 1,4-첨가 반응

2020년 8월

서울대학교 대학원

화학부 유기화학 전공

김창희

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A Thesis for M.S. Degree
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Department of Chemistry
The Graduate School
Seoul National University

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이 논문을 이학석사 학위논문으로 제출함

2020년 7월

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김창희의 석사 학위논문을 인준함

2020년 7월

위 원 장 김병문 (인)

부 위 원 장 이홍근 (인)

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Abstract

Cu-Catalyzed Enantioselective 1,4-Addition of 1,1-Bis[(pinacolato)boryl]methane

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A Cu-catalyzed enantioselective 1,4-addition of 1,1-bis[(pinacolato)boryl]methane to an α,β-unsaturated carbonyl system has been developed. This enantioselective reaction showed good to moderate yield and % *ee* on chalcone derivatives and other alkyl-substituted analogues. Moreover, the product, γ-borylated dihydrochalcone, could be employed to various further transformations with modifying its oxidation state. Finally, additive effect was investigated by employing ^{31}P and ^{11}B NMR.

Keywords: α,β-unsaturated carbonyl system, enantioselective, γ-borylated dihydrochalcone, 1,1-Bis[(pinacolato)boryl]methane.

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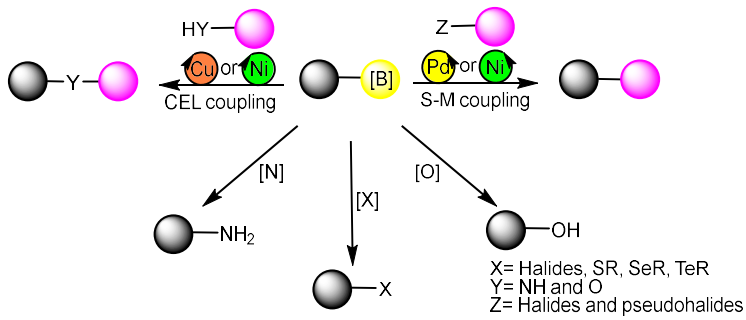
Contents

1. INTRODUCTION

Since H. Gilman revealed the structure of organocopper reagent and its basic reactivity in 1952,[1] organocopper has been studied to employ various electrophiles and nucleophiles and to conduct under milder conditions.[2] Among them, 1,4-addition reactions employing α,β-unsaturated carbonyl compounds as an electrophile have attracted attention.[3] It is because most other organo-metal nucleophiles show 1,2-addition selectivity, not 1,4-addition.

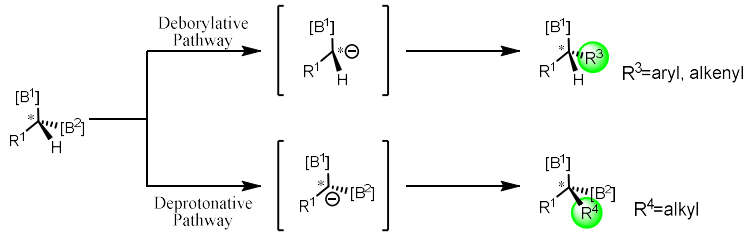
Organoboron is a class of the most utilized building blocks in the field of synthetic chemistry.[4] The compounds in this class have been studied on further transformation from C–B bonds into C–C or C–heteroatom bonds. Many methods to aminate, oxygenate and fluorinate them have been developed. However, from the development of Suzuki-Miyaura coupling reaction (S-M coupling),[5] organoborons started to get highlighted as coupling partner for $C(sp^2)$–$C(sp^2)$ to $C(sp^3)$–$C(sp^3)$ bond formation.[6] In addition to the C–C bond formation, researches on Chan-Evans-Lam coupling reaction (CEL coupling)[7] for C–O and C–N bond formation have been conducted to make conditions milder and improve functional group tolerance.[8] Employing heteroatoms other than O, N, and F[9] as coupling partners also has been attracted many organic chemists. In the same vein, organoborons got changed by introducing various protecting group to boronic acid; pinacol for general usage, 2,3-diaminonaphthalene to decrease reactivity, and potassium trifluorobarate to give photo-reactivity.[10]

Figure 1.1. Synthetic Versatility of Organoborons



As an option for synthesizing organoboron compounds, 1,1-bis(boryl) alkanes have got the limelight as valuable building blocks.[11] There are two major strategies to activate 1,1-bis(boryl) alkanes into nucleophiles (**Scheme 1.1**); 1) deborylation, and 2) deprotonation of the carbon with two boron moieties. In general, the first one is applied in transition-metal-catalyzed addition reactions[12] and cross coupling reactions.[13] The other one is applied to prepare other 1,1-bis(boryl) alkanes via S_N2 reactions or cross coupling reactions.[14]

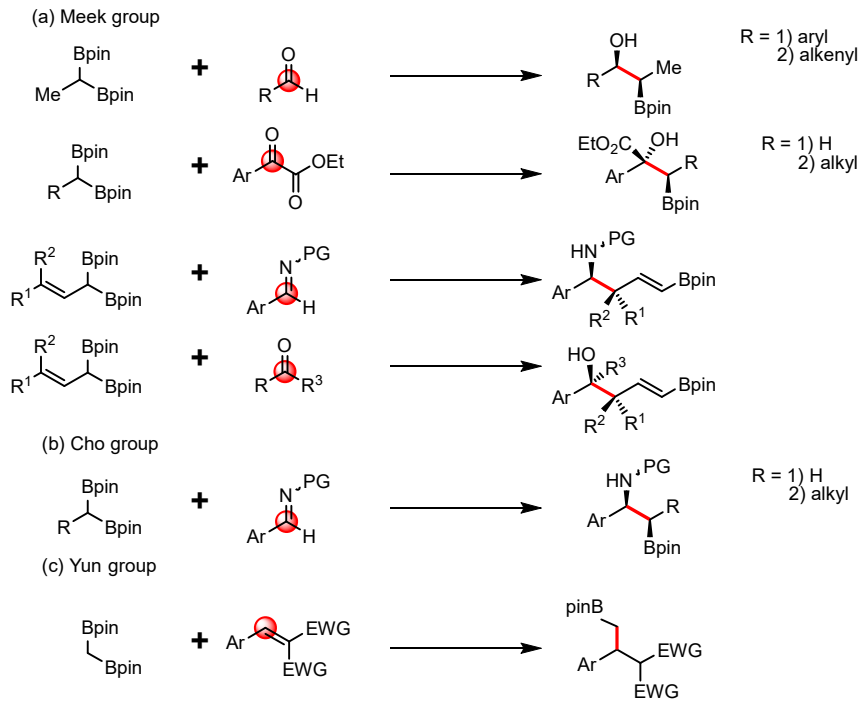
Scheme 1.1. Two Major Pathways to Activating 1,1-Bis(boryl) Alkanes



Representative examples of addition reactions following activation of 1,1-bis(boryl) alkanes via deborylative pathway included protocols of S. Meek and S. H. Cho. However, there was only one report on 1,4-addition by J. Yun[15] while 1,2-

addition reactions have been developed with employing various electrophiles such as aldehydes,[12d] aldimines,[12e-h] ketones,[12b] α-keto-esters,[12c] and imines[12i] (**Scheme 1.2**). Although it was noteworthy as the first example of enantioselective 1,4-addition reaction, still there was a limitation on substrate scope. The substrate was limited as diester, which is too un-reactive to be an electrophile of organocopper and makes β-carbon more electrophilic.

Scheme 1.2. Synthetic Application of 1,1-bis(boryl) alkanes

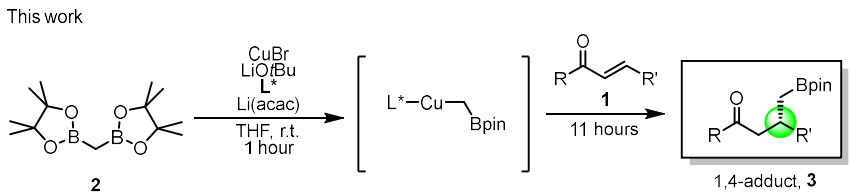


Chalcone is one of the most representative classes of α,β-unsaturated carbonyl compounds. This is because many SAR studies and patents have been reported on the anti-inflammatory and anti-ulcer potential of chalcone.[16] Also, chalcone could be easily prepared by Aldol condensation.[17] As well as chalcone itself, dihydrochalcone has been studied in the field of 1) pharmaceutics with its anti-microbial activity,[18]

anti-cancer,[19] and anti-oxidant,[20] and 2) food-industry as an artificial sweetener.[21]

To expand the utility of 1,1-bis(boryl) alkanes on 1,4-addition, we developed a method to synthesize enantio-enriched γ-borylated dihydrochalcone, containing a useful handle for further derivatizations. Easy-to-prepare chalcones and 1,1-bis[(pinacolato]boryl]methane **2** were employed as substrates and a precursor of nucleophile each (**Scheme 1.3**). As above examples, organocopper species is generated *in-situ* as a reactive nucleophile.[12g,15] Then, 1,4-addition reaction occurs on α,β-unsaturated carbonyl compound **1.**

Scheme 1.3. Strategy to Synthesize γ-Borylated Dihydrochalcone

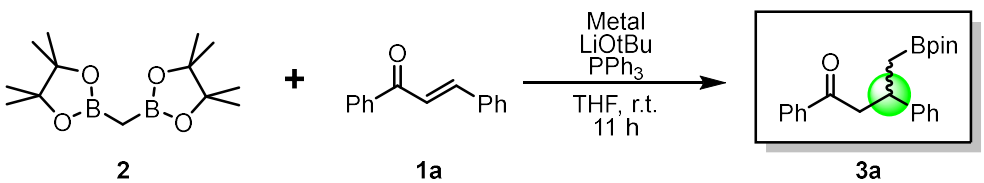


2. RESULTS AND DISCUSSION

2-1. Evaluations of Reaction Conditions

To optimize reaction conditions, various copper salts and silver salts were initially evaluated (**Table 2.1**). Cu(I) salts were employed for a pre-catalyst (entry 1-5). Among them, CuBr showed the best yield (entry 1). Cu(II) salts (entry 6-9) and silver(I) salts (entry 10-11) also gave low to moderate yields.

Table 2.1. Evaluation of the Reaction Conditions: Metal Sources[a]



2 **1a** **3a**

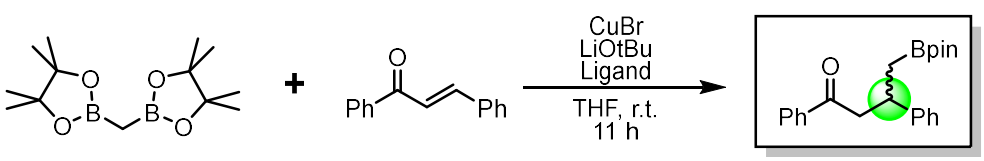
Entry	Metal	Base	Conversion (%)	Yield[b] (%)
1	CuBr	LiO*t*Bu	>99	45
2	CuI	LiO*t*Bu	>99	27
3	CuTC	LiO*t*Bu	70	32
4	CuOAc	LiO*t*Bu	65	13
5	CuCN	LiO*t*Bu	57	25
6	$Cu(CF_3\text{-acac})_2$	LiO*t*Bu	77	31
7	$Cu(OAc)_2$	LiO*t*Bu	>99	38
8	$CuBr_2$	LiO*t*Bu	>99	40
9	CuO	LiO*t*Bu	87	trace
10[c]	AgOTf	*n*BuLi	56	15
11[c]	AgOTf	NaO*t*Bu	95	37

[a]Reaction conditions: **2** (1.5 equiv.), metal (0.10 equiv.), PPh_3 (0.12 equiv.), LiO*t*Bu (1.2 equiv.), and **1a** (1.0 equiv., 0.17 M) in THF (0.6 mL).. [b]The yields of product were determined by gas chromatography with *n*-dodecane as an internal standard. [c]*n*BuLi (100 mol%) was used as base and

ligand was not used. [d]NaO*t*Bu (130 mol%) was used as base and ligand was not used.

With the result above, the ligand evaluation (**Table 2.2**) was carried out with CuBr as a pre-catalyst. Without ligand (entry 1), yield was lower than the case with PPh_3 (entry 3). The ligands evaluated were classified according to the atom participating in the coordination; 1) phosphine ligand (entry 2-8), 2) N-heterocycle (NHC) ligand (entry 9-11), 3) bipyridine ligand (entry 12 and 13), and 4) diamine ligand (entry 14). From the phosphine ligands, sterically bulky monodentate ligands showed low yield (entry 2 and 4). Bidentate ligands provided lower yield as their phosphorous centers were fixed by the backbone (entry 5-7). (±)-BINAP gave the best yield, compared to the results of the other achiral ligands (entry 8). All NHC ligands were not efficient in this reaction conditions (entry 9-11). Although bipyridine ligands showed high conversion, yields were still around 20% (entry 12 and 13). Diamine ligand showed low yield, similar to the results of bipyridines. At last, (S)-MONOPHOS, a phosphoramidite ligand, exhibited the best yield (entry 15).

Table 2.2. Evaluation of the Reaction Conditions: Ligands[a]

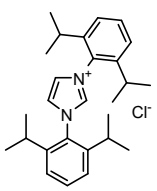


2 **1a** **3a**

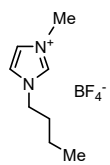
Entry	Ligand	Conversion (%)	Yield[b] (%)
1	-	>99	20
2	P*n*Bu$_3$	81	5
3	PPh_3	>99	45
4	Xphos	>99	25
5	dppb	>99	22

6	dppe	23	trace
7	dppf	61	trace
8	(±)-BINAP	>99	56
9	**NHC1**	<5	trace
10	**NHC2**	<5	trace
11	**NHC3**	<5	trace
12	**Bipyridine1**	>99	21
13	**Bipyridine2**	>99	18
14	**Diamine1**	61	20
15	(S)-MONOPHOS **(L1)**	98	63

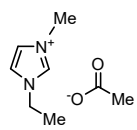
[a]Reaction conditions: **2** (1.5 equiv.), CuBr (0.10 equiv.), Ligand (0.12 equiv.), Li*O*t*Bu (1.2 equiv.), and **1a** (1.0 equiv., 0.17 M) in THF (0.6 mL). [b]The yields of product was determined by gas chromatography with *n*-dodecane as an internal standard.



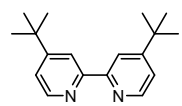
NHC1



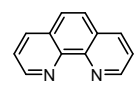
NHC2



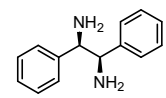
NHC3



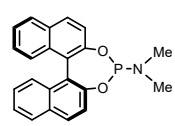
Bipyridine1



Bipyridine2



Diamine1

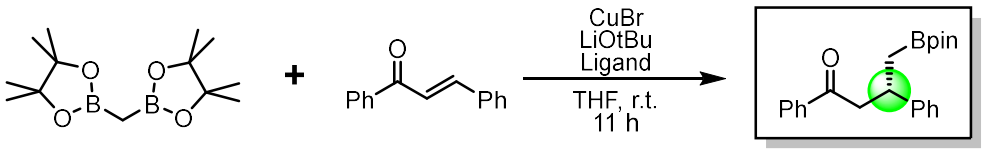


(S)-MONOPHOS (**L1**)

With the preliminary results on **Table 2.2**, further investigation on phosphoramidites was conducted (**Table 2.3**). **L1** showed the highest yield and enantiomeric excess (entry 1). Substituents adjacent to the nitrogen atom lowered both yield and enantiomeric excess (entry 2-4). Also, based on the results of entry 2 and entry 3, the substituents could not give an effect on facial selectivity. Methyl groups on BINAP-moiety showed low reactivity (entry 5). Both phosphoramidites with strained biphenyl and from TADDOL ligand failed to provide optimal results

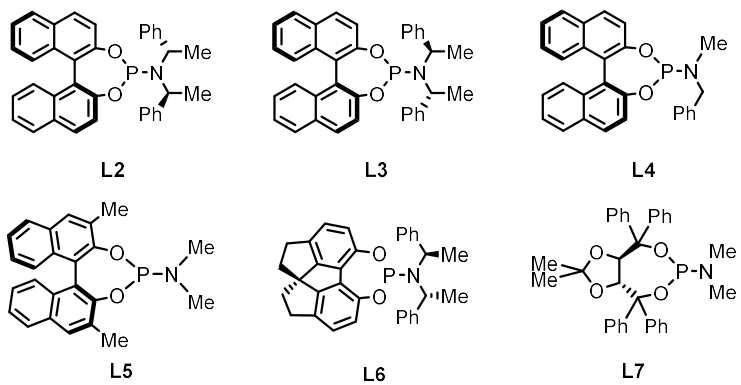
(entry 6 and 7).

Table 2.3. Evaluation of the Reaction Conditions: Phosphoramidites[a]



Entry	Ligand	Conversion (%)	Yield[b] (%)	ee (%)[c]
1	(S)-MONOPHOS (**L1**)	98	63	76
2	**L2**	74	19	6
3	**L3**	>99	26	8
4	**L4**	98	34	17
5	**L5**	>99	28	-1
6	**L6**	79	41	63
7	**L7**	98	40	4

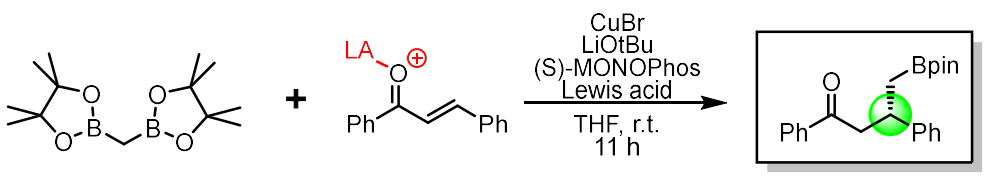
[a]Reaction conditions: **2** (1.5 equiv.), CuBr (0.10 equiv.), Ligand (0.12 equiv.), LiO*t*Bu (1.2 equiv.), and **1a** (1.0 equiv., 0.17 M) in THF (0.6 mL). [b]The yields of product was determined by gas chromatography with *n*-dodecane as an internal standard. [c]Enantiomeric excess (%ee) was determined by HPLC analysis employing chiral stationary phase.



At the last stage of optimization, various additives were evaluated. Actually, there was a preliminary result on additive effect on some Brønsted acid such as *t*butanol and methanol, which were generally employed as a proton source by other research

groups.[22] Since the Brønsted acids could not improve both yield and *ee*, this evaluation is only on the Lewis acids (**Table 2.4**). For convenience, the table contained the optimized result of **Table 2.3** (entry 1). Based on literatures, lithium salts were introduced to expect for lithium cation to activate carbonyl group as a Lewis acid (entry 2-4).[22] However, they could not improve the reaction on both yield and enantioselectivity. Even LiCl and LiBr significantly lowered yield and enantioselectivity. Other additives such as $BF_3 \bullet OEt_2$ (entry 5) and $ZnBr_2$ (entry 6) had no effect on the result neither. TMSCl, silicon-based Lewis acid, was also not efficient additive (entry 7). Only Li(acac) could increase both yield and enantioselectivity (entry 8). Yield and enantiomeric excess slightly decreased when the reaction scale went up to 0.3 mmol. Details on its effect would be elucidated in the last part of this section. Additionally, there was no significant changes on yield and enantioselectivity when 0.3 mmol of **1a** was used instead of 0.1 mmol or the concentration of **1a** in whole reaction mixture went up to 0.33 M.

Table 2.4. Evaluation of the Reaction Conditions: Lewis acids[a]



2 **1a** **3a**

Entry	Lewis acid (100 mol%)	Conversion (%)	Yield[b] (%)	ee (%)[c]
1	-	98	67	76
2	LiF	81	76	77
3	LiCl	30	29	<5
4	LiBr	28	28	<5

5	BF_3•OEt_2	<5	trace	-
6	$ZnBr_2$	<5	trace	-
7	TMSCl	36	24	7
8	Li(acac)	>99	74 (70)[d]	94 (92)[d]

[a]Reaction conditions: **2** (1.5 equiv.), CuBr (0.10 equiv.), **L1** (0.12 equiv.), Li*O*tBu (1.2 equiv.), additive (1.0 equiv.), and **1a** (1.0 equiv., 0.17 M) in THF (0.6 mL). [b]The yields of product was determined by gas chromatography with *n*-dodecane as an internal standard. [c]Enantiomeric excess (% ee) was determined by HPLC analysis employing chiral stationary phase. [d]0.3 mmol scale, determined after isolation.

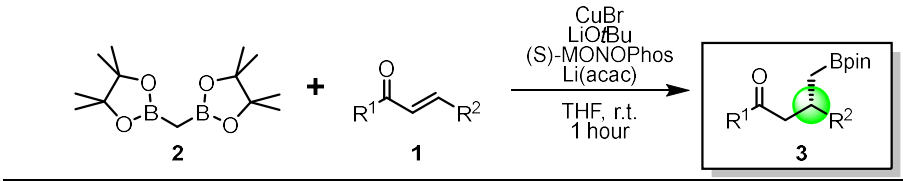
Based on the above evaluations, the optimized conditions were established as follows; 1) for catalyst generation, **2** (150 mol%), CuBr (10 mol%), **L1** (12 mol%), additive (100 mol%) and Li*O*tBu (120 mol%) were dissolved in 0.6 mL of THF and stirred for an hour, 2) **1a** (100 mol%, 0.3 mmol) was injected as 1M solution in THF and quenched after 11 hours by brine.

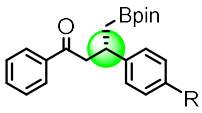
2-2. Substrate Scope

With the optimized reaction conditions in hand, the reactivity of the method by modifying substrates was evaluated (**Table 2.5**). At first, *trans*-chalcone **1a**, the most general form, gave the desired adduct **3a** with good yield and high % *ee*. Compared to **3a**, both electron-donating group (**3b**) and electron-withdrawing group (**3c** and **3d**) was afforded without significant loss on yield or % *ee*; in the case of **3b**, there was a loss on % *ee* to some extent. Then, steric hindrance on substrate itself was evaluated. Methyl group on *ortho*-position of styrenyl moiety gave a negative effect on yield (**3e**); it hindered the nucleophile from approaching. However, enantioselectivity kept up for this case. Methyl group on *meta*-position (**3f**), instead of *ortho*-position, also gave steric hindrance which was weaker than that *ortho*- one gave. On the other hand,

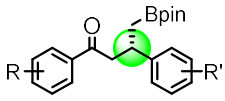
methyl group on *ortho*-position of ketone (**3g**) also decreased both yield and % *ee*. Then, α,β-unsaturated carbonyl compounds, other than chalcone derivatives, underwent the evaluation in same manner. All the furyl moieties on olefin afforded good yield and high % *ee* (**3h** and **3i**), regardless of their electronic property of the prochiral β-carbon. However, even with elongated reaction time, substrates with alkyl groups on olefin (**3j** and **3k**) afforded slightly lower yield and % *ee*. Also, the reaction was not effective at all for any other α,β-unsaturated carbonyl compounds with simple amide (**3l**), Weinreb amide (**3m**), ethyl ester (**3n**), trifluromethylketone (**3p**), and cyclohexylketone (**3p**). By elongating reaction time and elevating temperature, *t*Butylketone gave the desired product with moderate yield and low % *ee* (**3q**). Phenylsulfone was not tolerable in these conditions (**3r**). Finally, substituents on α- or β-carbon atom, even more than only proton, significantly interrupted this reaction (**3s** and **3t**). Byeong Do Roh significantly participated in this part (**3j**, **3k**, **3o–3r**).

Table 2.5. Substrate scope on α,β-Unsaturated Carbonyl Compounds

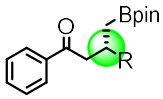




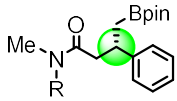
R =
1) H (**3a,** 70%, 92% *ee*)
2) OMe (**3b**, 68%, 85% *ee*)
3) Cl (**3c,** 76%, 94% *ee*)
4) F (**3d,** 77%, 91% *ee*)



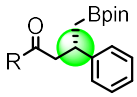
R, R' =
1) H, 2-Me (**3e,** 35%, 95% *ee*)
2) H, 3-Me (**3f,** 57%, 96% *ee*)
3) 2-Me, H (**3g,** 74%, 81% *ee*)



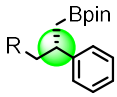
R =
1) 2-furyl (**3h,** 76%, 93% *ee*)
2) 3-furyl (**3i**, 74%, 93% *ee*)
3) cyclopropyl (**3j**[a]**,** 70%, 87% *ee*)
4) isopropyl (**3k**[a], 68%, 87% *ee*)



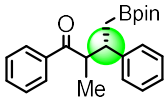
R =
1) Me (**3l,** n.d.)
2) OMe (**3m,** n.d.)



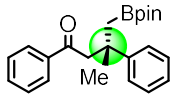
R =
1) OEt (**3n**, n.d.)
2) CF_3 (**3o,** n.d.)
3) cyclohexyl (**3p,** n.d.)
4) *t*Bu (**3q**[b]**,** 62%, 57% *ee*)



R =
1) SO_2Ph(**3r,** n.d.)



3s
n.d.



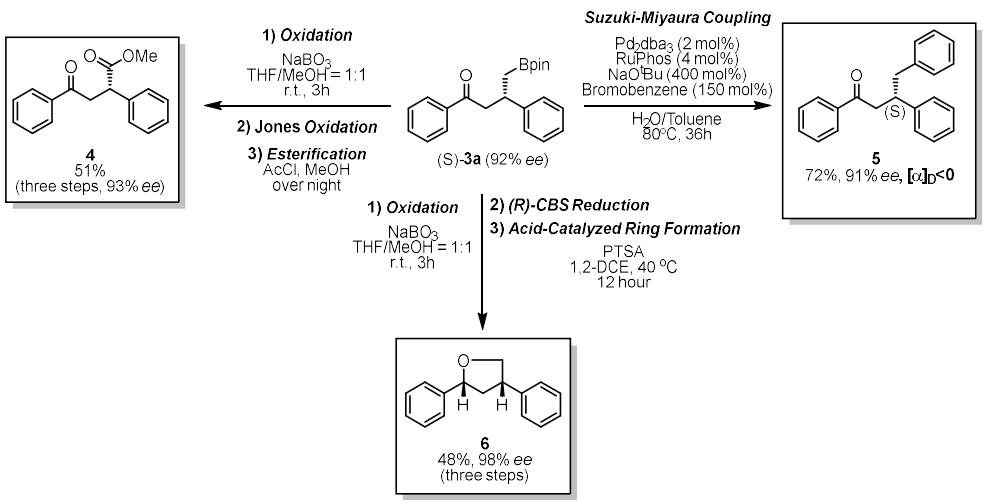
3t
n.d.

Reaction conditions: **2** (1.50 equiv.), CuBr (0.10 equiv.), (S)-MONOPhos (0.12 equiv.), Li(acac) (1.0 equiv.), LiO*t*Bu (1.20 equiv.), and **1a** (1.0 equiv. 0.3 mmol, 0.33 M) in THF (0.9 mL). [a]Reaction mixture was stirred for 36 hours. [b]Reaction mixure was stirred for 24 hours at 40 ℃.

2-3. Further Derivatizations

Enantio-enriched γ-borylated dihydrochalcone (S)-**3a** (92%ee) could play a role as a substrate for further derivatizations. To synthesize methyl ester **4**, C–B bond underwent oxidation to obtain alcohol. After the reaction completed, 2.5 M Jones reagent was added for the alcohol to oxidize into analogous carboxylic acid.[23] Then, acid-catalyzed esterification[24] gave **4** (51%, 93% *ee*) without a significant loss of enantiomeric excess. Second, Suzuki-Miyaura cross-coupling with bromobenzene was conducted. As a result, triphenylbutanone **5** (72%, 91% *ee*) was afforded with retained enantiomeric excess.[25] Compared to the reported optical rotation of **5**, the absolute configuration of the stereogenic center was determined as (S)-configuration. Finally, *ent*-calyxolane B **6** (48%, 98% *ee*) was synthesized from (S)-**3a** by conducting oxidation, (R)-CBS reduction,[26] and acid-catalyzed ring formation[24] in a serial order; excellent *ee* could be explained by Horeau's principle.[27]

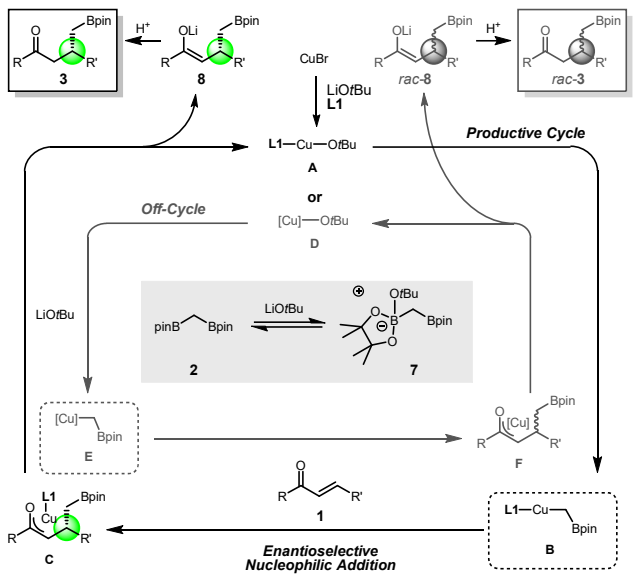
Scheme 2.1. Further Derivatizations



2-4. NMR Study on Additive Effect

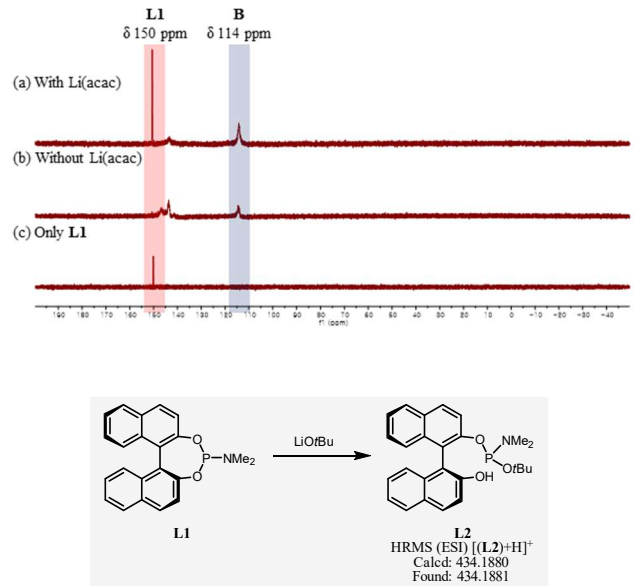
A plausible mechanism is proposed in **Scheme 2.2**. At first, an anion exchange occurs between CuBr and Li*O*t*Bu to afford catalyst **A**, following ligation of the chiral ligand (**L1**). Meanwhile, 2 is activated to be an ate-complex **7** by Li*O*t*Bu. Transmetalation between **A** and **7** affords a reactive organocopper species **B**. An enantioselective conjugate addition of **B** into enone **1** gives 1,4-adduct **C**. Chiral information is induced into the prochiral center, β-carbon of **1**, at this step. **C** is subsequently changed into lithium-enolate **8** via transmetalation with Li*O*t*Bu. Finally, protonation of **8** leads to γ-ketoboronic ester **3**. However, if **L1** undergoes the degradation,[28] the amount of **L1** would be insufficient for all CuBr to form **B**. That is, organocopper species **E** could be generated in spite of the excess amount of **L1** to CuBr.[15] **E** catalyzes the non-enantioselective conjugate addition to afford racemic intermediate **F**, which leads both yield and *ee* to decrease. Based on the mechanism and off-cycle, we conducted further studies on how Li(acac) enhances yield and enantioselectivity.

Scheme 2.2. The Plausible Mechanism



We investigated on the additive effect of Li(acac) by using ^{31}P NMR. **Figure 1** shows the signals of **L1** and **B**, presumed as a catalyst[12h]. In the absence of electrophile (**1**), signals of **B** appeared on the spectra from both condition (a) and (b) after induction period. Remains of **L1** after ligation should be detected since there were more of **L1** than CuBr. However, residual **L1** was detected only when Li(acac) was added. Furthermore, during the experiment, it was discovered that **L1** decomposed into **L2** and other unknown phosphorous species by ten-fold amount of LiOtBu; phosphoramidites could be modified by other alkoxides[29]. However, by coordinating to form Cu–**L1** complex, **L1** could avoid the decomposition to some extent. Additionally, **L2** exhibited no reactivity when **L2** was introduced in the optimized conditions instead of **L1**.

Figure 2.1. ^{31}P NMR Study on the Generation of B

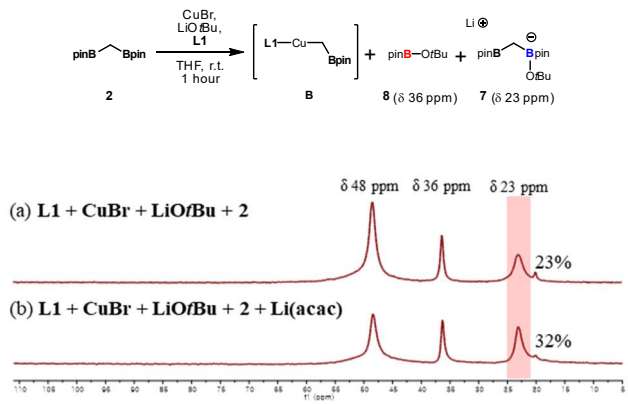


Conditions: (a) **L1** (1.0 eq., 0.024 M), **2** (12.5 eq.), CuBr (0.83 eq.), LiO*t*Bu (10 eq.), and Li(acac) (8.3 eq.) in THF-d_8 (0.5 mL), (b) **L1** (1.0 eq., 0.024 M), **2** (12.5 eq.), CuBr (0.83 eq.), and LiO*t*Bu (10 eq.) in THF-d_8 (0.5 mL), (c) **L1** (1.0 eq., 0.024 M) in THF-d_8 (0.5 mL)

After finding that the ligand degradation is primarily suppressed by ligation to CuBr, the focus was moved to where stoichiometric amount of LiO*t*Bu would be consumed (**Figure 2.2**). When there were only **2** and LiO*t*Bu in THF, the mole fraction of borate complex **7** was proportional to approximately 88% of the equivalence of the base[30]. However, when stoichiometric amount of Li(acac) was added, the mole fraction went up to over 95%; almost quantitative amount of bases participates in the formation of **7**. There are three major peaks on the spectra; δ 48 ppm, 36 ppm, and 23 ppm. The borate (δ 36 ppm), a byproduct of the transmetalation between **A** and **2**, was produced at most the amount of CuBr in both conditions. By comparing the area ratio of the peak (δ 23 ppm) to the whole integration of the three peaks, it could be

suggested that the formation of **7** would be facilitated by adding Li(acac). In summary, the ligand degradation, which decreases yield and *ee*, would be suppressed by the factors; (major) ligation to CuBr, and (minor) moved equilibrium between **2** and **7** to consume LiO*t*Bu.

Figure 2.2. ^{31}P NMR Study on Effect of Li(acac)



Conditions: (a) **L1** (1.0 eq., 0.024 M), **2** (12.5 eq.), CuBr (0.83 eq.), and LiO*t*Bu (10 eq.) in THF-d_8 (0.5 mL), (b) **L1** (1.0 eq., 0.024 M), **2** (12.5 eq.), CuBr (0.83 eq.), LiO*t*Bu (10 eq.), and Li(acac) (8.3 eq.) in THF-d_8 (0.5 mL).

3. CONCLUSION

In conclusion, an enantioselective conjugate addition reaction of 1,1-bis[(pinacolato)boryl]methane to more general α,β-unsaturated carbonyl compounds was developed. While conducting the study, we found that the chiral ligand would be degraded under basic conditions, which leads both yield and *ee* to decrease. To solve this problem, we introduced Li(acac) as an additive and successfully prevented the degradation of the chiral ligand. Furthermore, the additive effect was elucidated by employing ^{11}B and ^{31}P NMR analysis.

4. EXPERIMENTAL SECTION

General experimental details

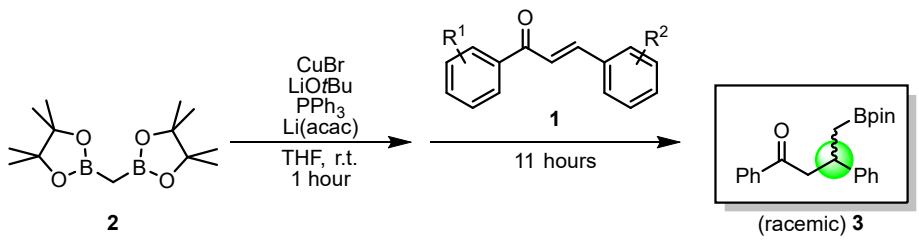
Unless stated, all reagents were weighed in glove box and taken away under seal in oven-dried 4 mL dram-vial. Anhydrous tetrahydrofuran (THF) was degassed by sonication under light vacuum after dried by a solvent purification system. In most cases, reagents were purchased from Sigma Aldrich, TCI, Alfa Aesar, Acros, Fluka and Strem with the reasonable grade and used without any additional purification. For bulk purchases, 1,1-bis[(pinacolato)boryl]methane and (S)-MONOPHOS were obtained from Angene and Chemscene each. Yields represent isolated yield. All spectral data were acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR) for $CDCl_3$, was used as a reference. For heteroatom NMR, 15% $BF_3 \bullet OEt_2$ solution in $CDCl_3$ (0 ppm) and 85% H_3PO_4 solution in H_2O (0 ppm) were used as external standards for obtaining each ^{11}B and ^{31}P NMR. For ^{19}F NMR, fluorobenzene was used as an internal standard (-113.15 ppm). Coupling constants (*J*) are reported in Hertz (Hz) to the nearest 0.1 Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR spectra were recorded on an Agilent 400-MR DD2 Magnetic Resonance System or Varian/Oxford As-500 instrument and calibrated using residue undeuterated solvent as internal reference. Reactions were monitored by thin-layers chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F 254) using UV light or staining solution such as potassium permangate and *p*-anisaldehyde. Stationary phase of flash column chromatography was Silica gel (60, particle size 0.040–0.063 mm) from E. Merck. Enantiomeric excesses (% *ee*) were

determined by employing High-Performance Liquid Chromatography (HPLC) with columns containing chiral stationary phase and HPLC-grade eluents (hexane and isopropanol). Unless there was any special mentions, HPLC equipment was C196-E061W (Shimadzu, degassing unit : DGU-20A5R, pump : LC-20AD, auto sampler : SIL-20A, communication bus module : CBM-20A, UV/Vis detector : SPD-20A, and column oven : CTO-20A). Other information such as column, wavelength of light, temperature, flow rate, eluent, and retention time was specified respectively. Optical rotations measured by JASCO P1030 polarimeter (D line of sodium vapor lamp) with a cylindrical glass cell from the same company.

Preparation of the chalcone derivatives 1a-1q

Aldol condensation followed by recrystallization was proceeded to prepare chalcone derivatives **1a**-**1j**, and **1q.**[31] **1k** was synthesized via Wittig olefination.[32]

General procedure for syntheses of racemic 3a~z

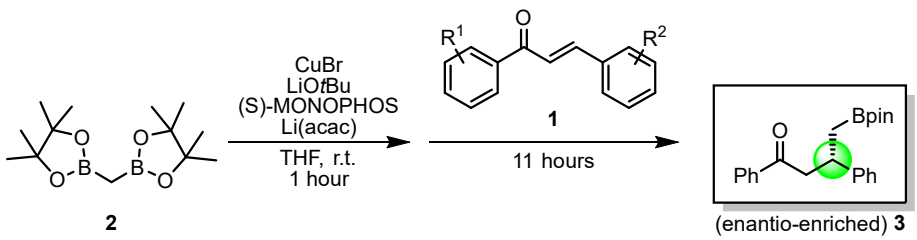


For compounds racemic **3a-z.**

In a nitrogen-filled glove box, 4 mL dram-vial was filled with CuBr (0.030 mmol, 10 mol%, 4.2 mg), PPh_3 (0.036 mmol, 12 mol%, 9.6 mg), LiO*t*Bu (0.36 mmol, 120 mol%, 28.8 mg) and 1,1-bis[(pinacolato)boryl]methane (**2**, 0.45 mmol, 150 mol%, 120.6 mg), Li(acac) (0.30 mmol, 100 mol%, 31.8 mg) in THF (0.6 mL). Before getting out the vial from the glove box, the vial was sure to be sealed. After an hour, *trans*-chalcone (**1**, 0.3 mmol, 100 mol%, 62.4 mg) in THF (0.3 mL) was injected into the dram-vial. The reaction mixture was stirred in r.t for 11 hours.

To purify the product, brine was added as a quencher. After quenching, the solution was extracted with EA and brine. The organic layer, which was dried by Na_2SO_4, was concentrated *in vacuo*. The concentrated crude mixture was purified by flash column chromatography (Hexanes : DCM = 100 : 0 → Hexanes : DCM = 5 : 95); non-polar impurities were removed by rapidly increasing the proportion of DCM (Hexanes : DCM = 100 : 0 → Hexanes : DCM = 20 : 80). In the case with R_f less than 0.3 (TLC developed by DCM), methanol was added up to 3% in DCM after the column was filled with only DCM.

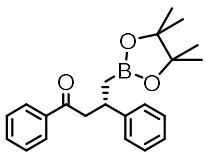
General procedure for syntheses of enantio-enriched 3a~z



For compounds racemic **3a-z.**

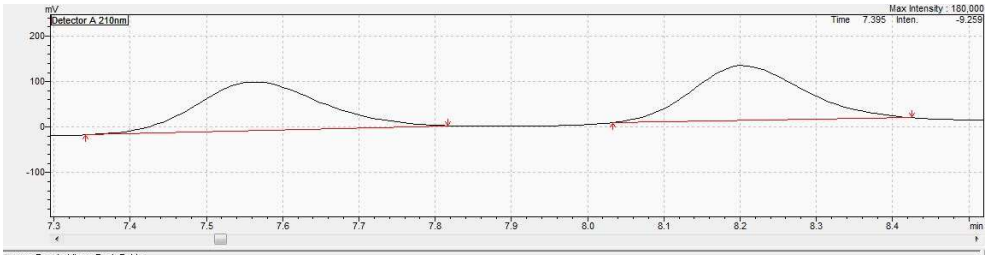
In a nitrogen-filled glove box, 4 mL dram-vial was filled with CuBr (0.030 mmol, 10 mol%, 4.2 mg), (S)-MONOPHOS (0.036 mmol, 12 mol%, 12.9 mg), LiO*t*Bu (0.36 mmol, 120 mol%, 28.8 mg) and **2** (0.45 mmol, 150 mol%, 120.6 mg), Li(acac) (0.30 mmol, 100 mol%, 31.8 mg) in THF (0.6 mL). Before getting out the vial from the glove box, the vial was sure to be sealed. After an hour, **1** (0.3 mmol, 100 mol%, 62.4 mg) in THF (0.3 mL) was injected into the dram-vial. The reaction mixture was stirred in r.t for 11 hours.

To purify the product, brine was added as a quencher. After quenching, the solution was extracted with EA and brine. The organic layer, which was dried by Na_2SO_4, was concentrated *in vacuo*. The concentrated crude mixture was purified by flash column chromatography (Hexanes : DCM = 100 : 0 → Hexanes : DCM = 5 : 95); non-polar impurities were removed by rapidly increasing the proportion of DCM (Hexanes : DCM = 100 : 0 → Hexanes : DCM = 20 : 80). In the case with R_f less than 0.3 (TLC developed by DCM), methanol was added up to 3% in DCM after the column was filled with only DCM.



(S)-1,3-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3a**)

Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 →5 : 95) to obtain **3a** as a yellowish liquid (74 mg, 70%, 92% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.54 – 7.48 (m, 1H), 7.45 – 7.37 (m, 2H), 7.31 – 7.20 (m, 4H), 7.17 – 7.09 (m, 1H), 3.62 (dq, *J* = 14.1, 7.0 Hz, 1H), 3.38 – 3.19 (m, 2H), 1.28 (ddd, *J* = 24.2, 15.5, 7.8 Hz, 2H), 1.09 (d, *J* = 8.7 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 146.3, 137.2, 132.7, 128.4, 128.2, 128.1, 127.2, 126.1, 83.0, 47.7, 37.3, 24.7, 24.6. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.5; HRMS (ESI) calculated for $[C_{22}H_{27}BO_3+H]^+$: 351.2126, found: 351.2138; 92% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 °C); t_R = 7.60 min (major), t_R = 8.21 min (minor); $[\alpha]_D^{22}$ = -7.9 (c = 1.04, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

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1	7.563	1221868	106891	M	50.095				50.095
2	8.204	1217253	120299	M	49.905				49.905
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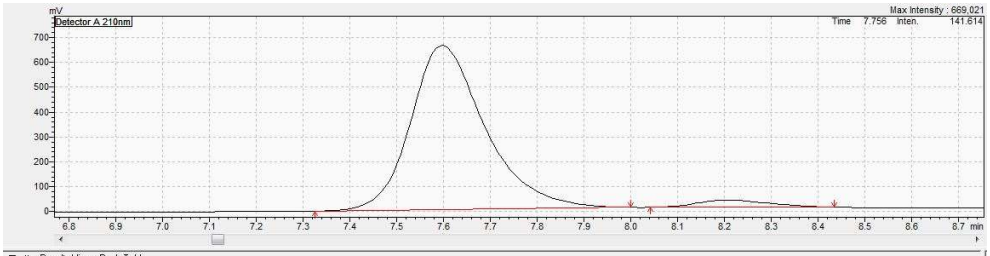
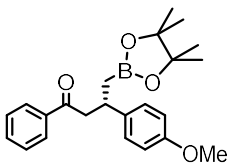


Results View - Peak Table

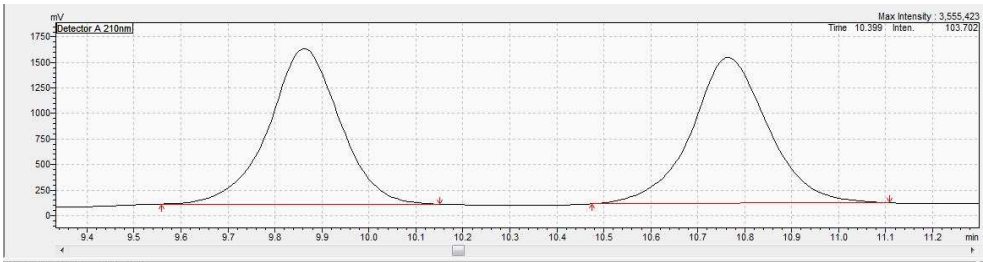
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	7.597	7320598	660736	M	95.895				95.895
2	8.206	313345	29591	M	4.105				4.105
Total		7633943	690327		100.000				100.000



(S)-3-(4-methoxyphenyl)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3b**)

Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 98 : 2) to obtain **3b** as a yellowish liquid (75 mg, 68%, 85% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.55 – 7.49 (m, 1H), 7.45 – 7.38 (m, 2H), 7.21 – 7.14 (m, 2H), 6.82 – 6.76 (m, 2H), 3.75 (s, 3H), 3.56 (tt, *J* = 14.3, 7.1 Hz, 1H), 3.25 (qd, *J* = 15.9, 7.1 Hz, 2H), 1.29 (dd, *J* = 15.5, 6.9 Hz, 1H), 1.19 (dd, *J* = 15.5, 8.8 Hz, 1H), 1.10 (d, *J* = 7.7 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.29, 157.88, 138.52, 137.29, 132.72, 128.43, 128.18, 128.17, 113.60, 83.03, 55.21, 48.01, 36.65, 24.75, 24.63. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.3; HRMS (ESI) calculated for $[C_{23}H_{29}BO_4+H]^+$: 369.2032, found: 369.2044; 85% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 °C); t_R = 9.86 min (major), t_R = 10.80 min (minor); $[\alpha]_D^{22}$ = +3.98 (c = 0.58, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

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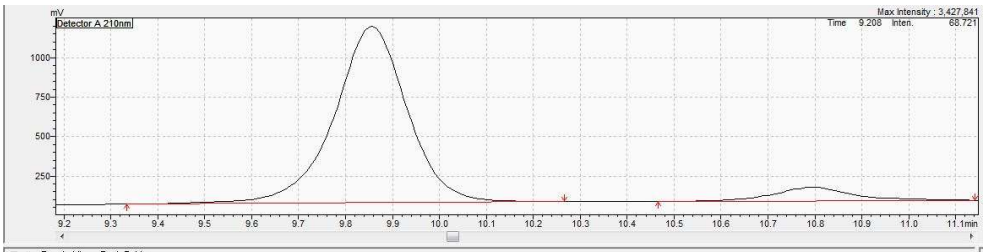
2	10.764	16234816	1431284	M	50.367				50.367
Total		32233142	2952592		100.000				100.000



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

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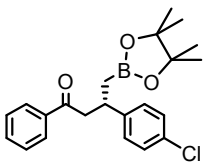
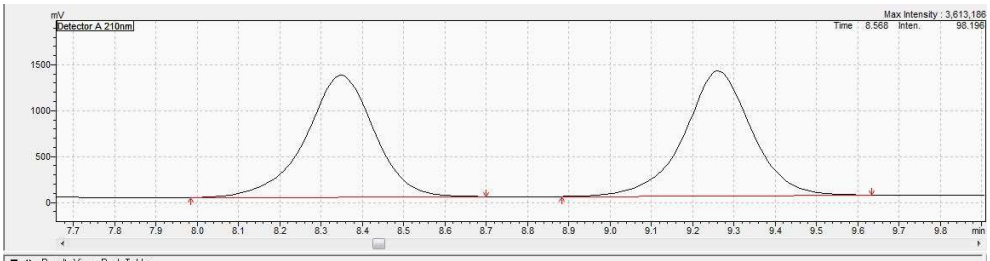
2	10.795	1015910	85216	M	7.713				7.713
Total		13171651	1202398		100.000				100.000



(S)-3-(4-chlorophenyl)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3c**)

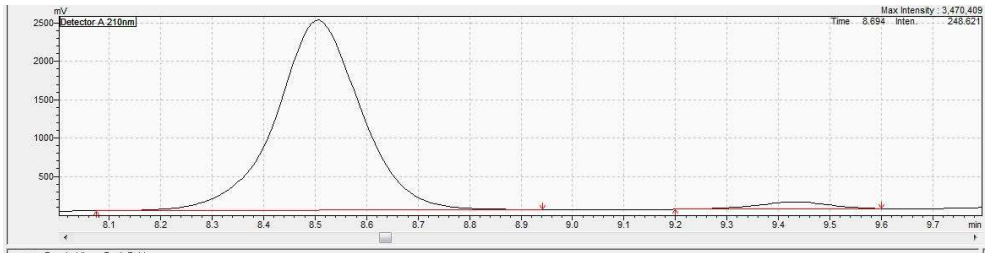
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 99 : 1) to obtain **3c** as a yellowish liquid (86 mg, 76%, 94% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.85 (m, 2H), 7.57 – 7.49 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.20 (s, 4H), 3.65 – 3.54 (m, 1H), 3.27 (qd, *J* = 16.3, 7.1 Hz, 2H), 1.30 (dd, *J* = 15.6, 6.8 Hz, 1H), 1.19 (dd, *J* = 15.6, 8.7 Hz, 1H), 1.11 (d, *J* = 9.1 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.73, 144.86, 137.08, 132.87, 131.65, 128.69, 128.47, 128.27, 128.07, 83.14, 47.46, 36.67, 24.72, 24.60. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.2; HRMS (ESI) calculated for $[C_{22}H_{26}BClO_3+H]^+$: 381.2232, found: 381.2240; 94% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 ºC); t_R = 8.51 min (major), t_R = 9.43 min (minor); $[\alpha]_D^{22}$ = -3.42 (c = 0.99, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

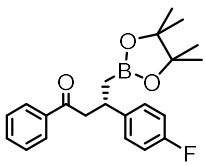
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	8.349	15321225	1329103	M	49.808				49.808
2	9.261	15439537	1356526	M	50.192				50.192
Total		30760762	2685629		100.000				100.000



Results View - Peak Table

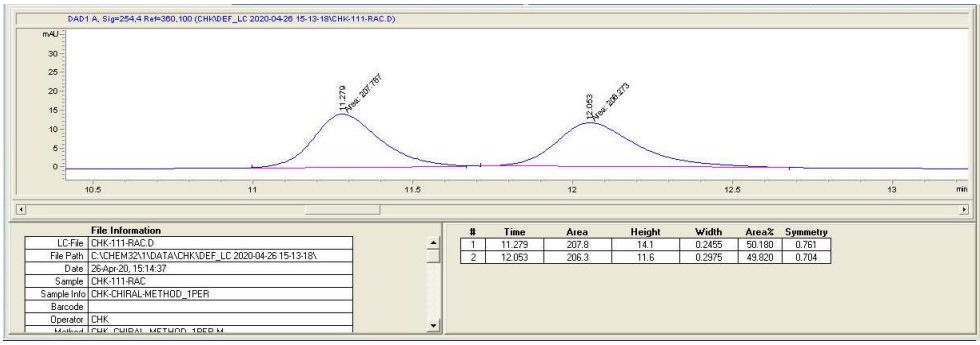
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	8.505	28524221	2478403	M	96.990				96.990
2	9.433	885169	89653	M	3.010				3.010
Total		29409390	2568056		100.000				100.000



(S)-3-(4-fluorophenyl)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3d**)

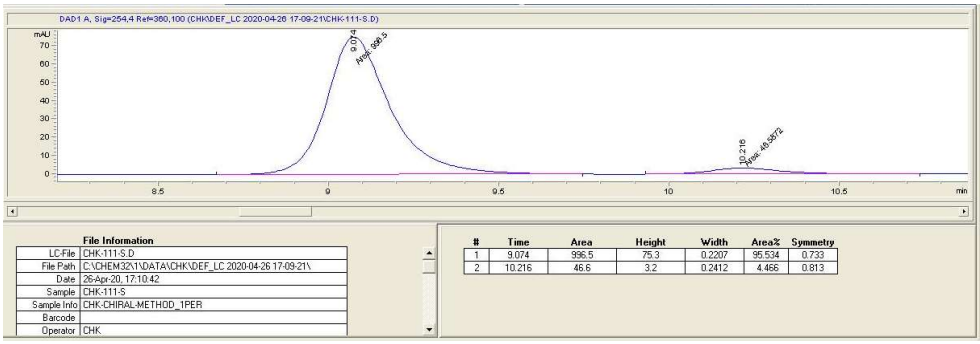
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 99 : 1) to obtain **3d** as an orange liquid (89 mg, 77%, 91% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.86 (m, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.22 (dd, *J* = 8.6, 5.5 Hz, 2H), 6.92 (t, *J* = 8.7 Hz, 2H), 3.67 – 3.55 (m, 1H), 3.26 (qd, *J* = 16.1, 7.1 Hz, 2H), 1.30 (dd, *J* = 15.5, 6.7 Hz, 1H), 1.20 (dd, *J* = 15.5, 9.0 Hz, 1H), 1.10 (d, *J* = 9.1 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.92, 161.27 (d, *J* = 243.6 Hz), 141.96 (d, *J* = 3.2 Hz), 137.15, 132.83, 128.70 (d, *J* = 7.8 Hz), 128.46, 128.09, 114.87 (d, *J* = 21.1 Hz), 83.09, 47.79, 36.64, 24.71, 24.59. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.38. HRMS (ESI) calculated for $[C_{22}H_{26}BFO_3+H]^+$: 369.2032, found: 369.2044; 91% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 254 nm, 30 °C); t_R = 9.07 min (major), t_R = 10.22 min (minor); $[\alpha]_D^{22}$ = -0.85 (c = 1.50, DCM).



File Information

LC-File	CHK-111-RAC.D
File Path	C:\CHEM32\1\DATA\CHK\DEF_LC 2020-04-26 15-13-18\
Date	26-Apr-20, 15:14:37
Sample	CHK-111-RAC
Sample Info	CHK-CHIRAL-METHOD_1PER
Barcode	
Operator	CHK

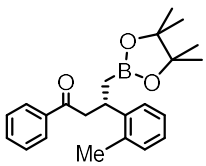
#	Time	Area	Height	Width	Area%	Symmetry
1	11.279	207.8	14.1	0.2455	50.180	0.761
2	12.053	206.3	11.6	0.2975	49.820	0.704



File Information

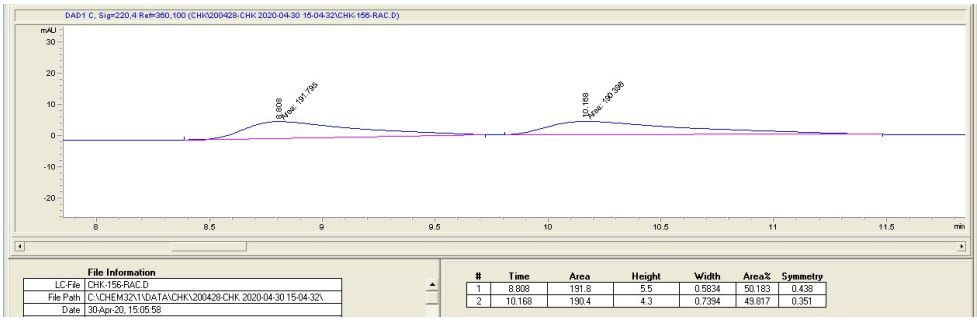
LC-File	CHK-111-S.D
File Path	C:\CHEM32\1\DATA\CHK\DEF_LC 2020-04-26 17-09-21\
Date	26-Apr-20, 17:10:42
Sample	CHK-111-S
Sample Info	CHK-CHIRAL-METHOD_1PER
Barcode	
Operator	CHK

#	Time	Area	Height	Width	Area%	Symmetry
1	9.074	996.5	75.3	0.2207	95.534	0.733
2	10.216	46.6	3.2	0.2412	4.466	0.813



(S)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(o-tolyl)butan-1-one (**3e**)

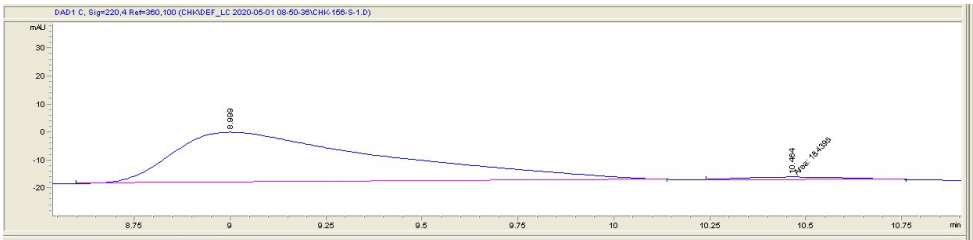
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 99 : 1) to obtain **3e** as a yellowish liquid (38 mg, 35%, 95% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.20 – 6.99 (m, 3H), 3.87 (dq, *J* = 13.9, 6.9 Hz, 1H), 3.37 – 3.15 (m, 2H), 2.39 (s, 3H), 1.29 (dd, *J* = 15.4, 6.6 Hz, 1H), 1.21 (dd, *J* = 15.4, 9.4 Hz, 1H), 1.04 (d, *J* = 12.4 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.29, 144.66, 137.30, 135.70, 132.76, 130.15, 128.44, 128.12, 126.05, 125.77, 125.76, 82.96, 47.45, 32.01, 24.57, 19.76. The carbon bound to the boron was not detected due to quadrupolar relaxation. Carbons of methyl groups of the pinacol moiety were represented as one peak (24.57). ^{11}B (128 MHz, $CDCl_3$) δ 33.0; HRMS (ESI) calculated for $[C_{23}H_{29}BO_3 + H]^+$: 365.2283, found: 365.2296; 95% *ee* was measured by HPLC (CHIRALCEL OD-H, *n*-hexane : *i*-PrOH = 99.2, 1.0 mL/min, wavelength = 220 nm, 30 °C); t_R = 9.00 min (major), t_R = 10.46 min (minor); $[\alpha]_D^{22}$ = -2.0 (c = 0.76, DCM).



File Information

LC-File	CHK-156-RAC.D
File Path	C:\CHEM32\1\DATA\CHK\200428-CHK 2020-04-30 15-04-32\
Date	30-Apr-20, 15:05:58

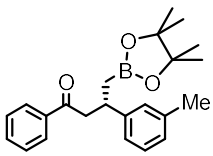
#	Time	Area	Height	Width	Area%	Symmetry
1	8.809	191.8	5.5	0.5834	50.183	0.438
2	10.168	190.4	4.3	0.7394	49.817	0.351



File Information

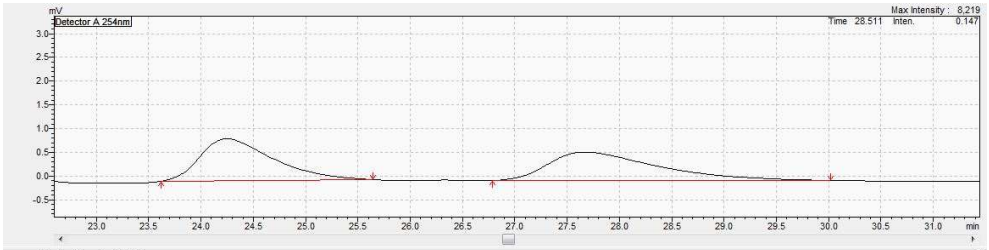
LC-File	CHK-156-S-1.D
File Path	C:\CHEM32\1\DATA\CHK\DEF_LC 2020-05-01 08-50-36\
Date	01-May-20, 08:51:47

#	Time	Area	Height	Width	Area%	Symmetry
1	8.999	683.8	18	0.536	97.374	0.344
2	10.464	18.4	9.6E-1	0.3192	2.626	0.86



(S)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(*m*-tolyl)butan-1-one (**3f**)

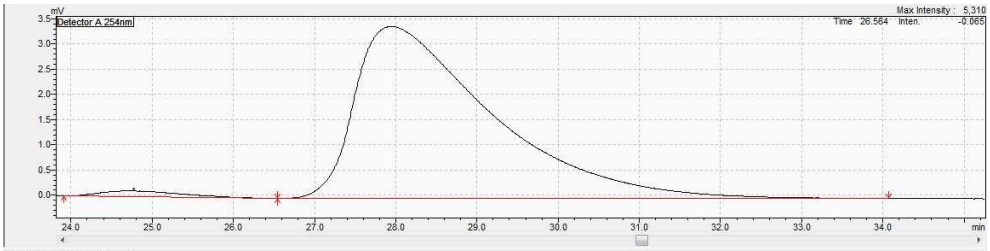
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 99 : 1) to obtain **3f** as a yellowish liquid (62 mg, 57%, 96% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.56 – 7.49 (m, 1H), 7.47 – 7.38 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.03 (m, 2H), 6.96 (d, *J* = 7.2 Hz, 1H), 3.64 – 3.52 (m, 1H), 3.37 – 3.21 (m, 2H), 2.30 (s, 3H), 1.31 (dd, *J* = 15.5, 6.8 Hz, 1H), 1.21 (dd, *J* = 15.5, 8.8 Hz, 1H), 1.10 (d, *J* = 8.7 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.17, 199.17, 146.32, 137.56, 137.29, 132.70, 128.39, 128.14, 128.10, 128.10, 126.80, 124.16, 82.97, 77.32, 77.00, 76.68, 47.63, 37.22, 24.69, 24.60, 21.41. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.0; HRMS (ESI) calculated for $[C_{23}H_{29}BO_3+H]^+$: 365.2283, found: 365.2293; 96% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 99.8 : 0.2, 1.0 mL/min, wavelength = 254 nm, 30 ºC); t_R = 24.73 min (major), t_R = 24.95 min (minor); $[\alpha]_D^{22}$ = +4.7 (c = 1.23, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

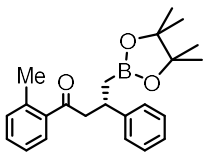
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	24.250	42929	883	M	49.796				49.796
2	27.682	43281	598	M	50.204				50.204
Total		86210	1481		100.000				100.000



Results View - Peak Table

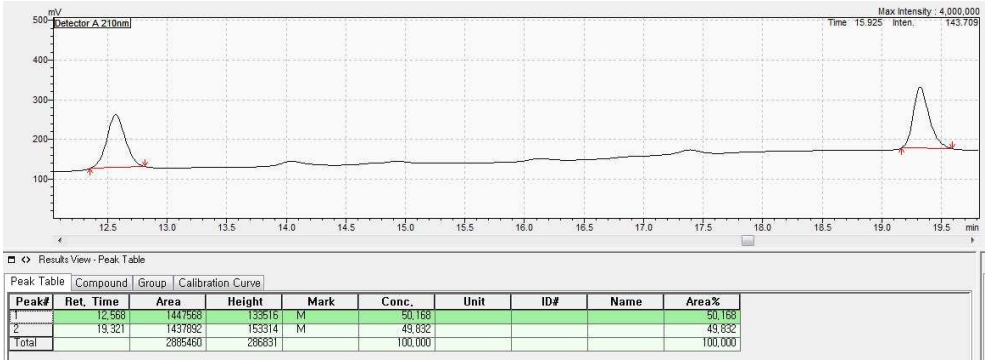
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	24.730	8528	120	M	2.093				2.093
2	27.955	398932	3414	M	97.907				97.907
Total		407460	3534		100.000				100.000



(S)-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(o-tolyl)butan-1-one (**3g**)

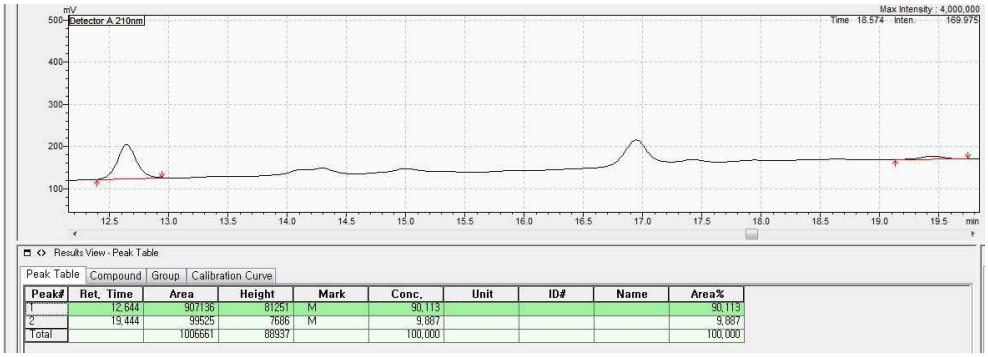
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100) to obtain **3g** as a yellowish liquid (81 mg, 74%, 81% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.31 (td, *J* = 7.5, 1.1 Hz, 1H), 7.27 – 7.10 (m, 7H), 3.60 – 3.48 (m, 1H), 3.22 (ddd, *J* = 24.1, 16.0, 7.3 Hz, 2H), 2.26 (s, 3H), 1.29 (dd, *J* = 15.5, 7.0 Hz, 1H), 1.21 (dd, *J* = 15.5, 8.7 Hz, 1H), 1.10 (d, *J* = 6.7 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.72, 146.01, 138.59, 137.78, 131.66, 130.79, 128.19, 128.15, 127.34, 126.12, 125.41, 83.04, 50.79, 37.58, 24.71, 24.64, 20.71. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.0; HRMS (ESI) calculated for $[C_{23}H_{29}BO_3+H]^+$: 365.2283, found: 365.2296; 81% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 ºC); t_R = 12.64 min (major), t_R = 19.44 min (minor); $[\alpha]_D^{22}$ = -2.6 (c = 1.05, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

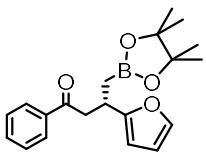
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	12.568	1447568	133515	M	50.168				50.168
2	19.321	1437892	153314	M	49.832				49.832
Total		2885460	286831		100.000				100.000



Results View - Peak Table

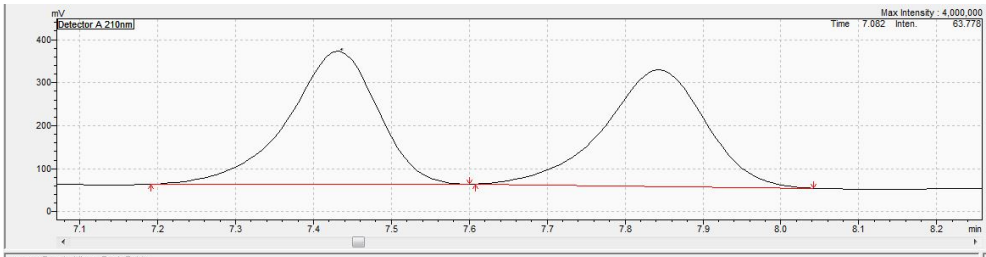
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	12.644	907136	81251	M	90.113				90.113
2	19.444	99525	7686	M	9.887				9.887
Total		1006661	88937		100.000				100.000



(S)-3-(furan-2-yl)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3h**)

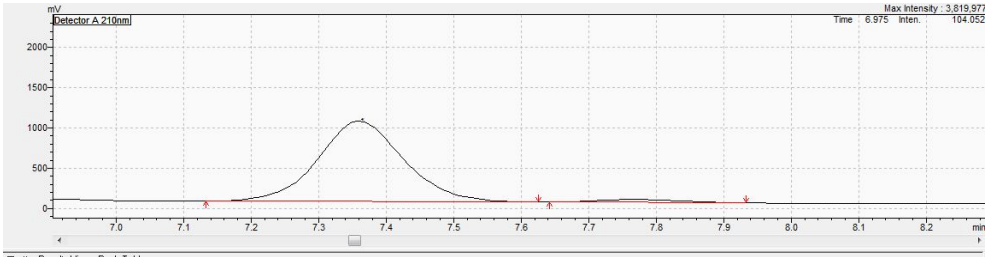
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 99 : 1) to obtain **3h** as a yellowish liquid (77 mg, 76%, 93% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.88 (m, 2H), 7.58 – 7.51 (m, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.22 (m, 1H), 6.24 – 6.20 (m, 1H), 6.02 (d, *J* = 3.2 Hz, 1H), 3.73 (p, *J* = 7.1 Hz, 1H), 3.32 (ddd, *J* = 48.1, 16.3, 6.9 Hz, 2H), 1.26 (d, *J* = 7.3 Hz, 2H), 1.19 (d, *J* = 7.9 Hz, 12H). ^{13}C NMR (101 MHz, CDCl3) δ 198.86, 159.11, 140.68, 137.19, 132.82, 128.44, 128.15, 109.87, 104.26, 83.13, 44.68, 30.79, 24.78, 24.70. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.1; HRMS (ESI) calculated for $[C_{20}H_{25}BO_4+H]^+$: 341.1919, found: 341.1930; 93% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 ºC); t_R = 7.36 min (major), t_R = 7.70 min (minor); $[\alpha]_D^{22}$ = -9.5 (c = 0.79, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

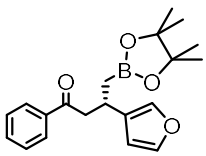
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	7.431	2474196	309226	M	50.240				50.240
2	7.843	2450574	271402	M	49.760				49.760
Total		4924771	580628		100.000				100.000



Results View - Peak Table

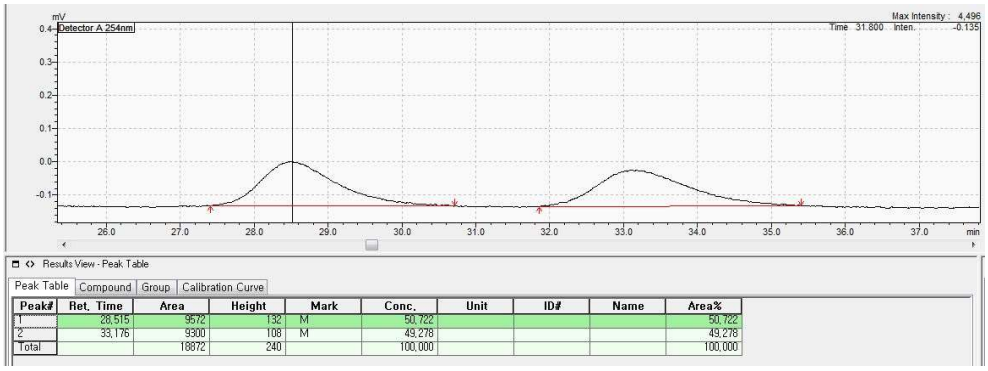
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	7.359	8834941	1000458	M	96.637				96.637
2	7.769	307501	36845	M	3.363				3.363
Total		9142441	1037303		100.000				100.000



(S)-3-(furan-3-yl)-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3i**)

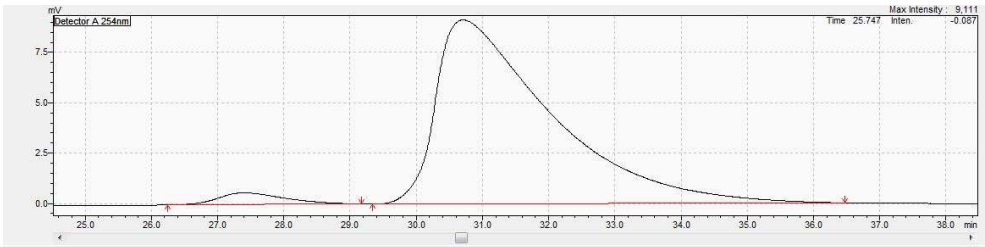
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100, then DCM : MeOH = 100 : 0 → 99 : 1) to obtain **3i** as a yellowish liquid (76 mg, 74%, 93% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.29 (s, 1H), 7.24 (s, 1H), 6.33 (d, *J* = 0.4 Hz, 1H), 3.56 (dd, *J* = 14.6, 7.2 Hz, 1H), 3.21 (ddd, *J* = 23.6, 16.1, 7.0 Hz, 2H), 1.22 (dd, *J* = 15.6, 9.0 Hz, 2H), 1.16 (d, *J* = 6.3 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.21, 142.56, 138.50, 137.28, 132.82, 129.90, 128.47, 128.15, 109.67, 83.13, 46.95, 27.86, 24.76, 24.68. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.1; HRMS (ESI) calculated for $[C_{20}H_{25}BO_4+H]^+$: 341.1919, found: 341.1921; 93% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 99.8:0.2, 1.0 mL/min, wavelength = 254 nm, 30 ºC); t_R = 30.71 min (major), t_R = 27.41 min (minor); $[\alpha]_D^{22}$ = +0.59 (c = 0.71, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

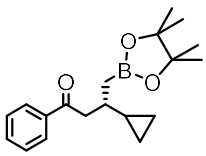
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	28.515	9572	132	M	50.722				50.722
2	33.176	9300	108	M	49.278				49.278
Total		18872	240		100.000				100.000



Results View - Peak Table

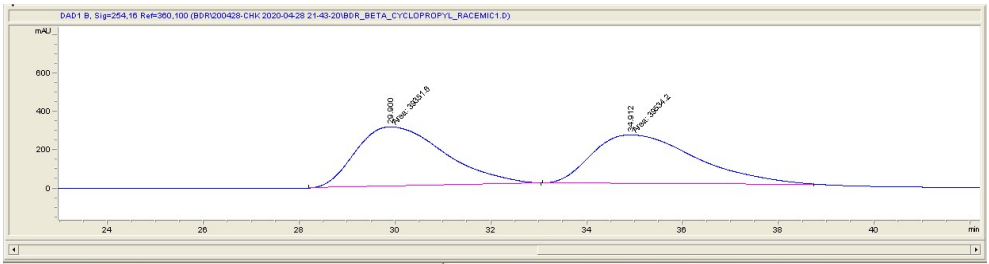
Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	27.410	41019	583	M	3.573				3.573
2	30.705	1107060	9133	M	96.427				96.427
Total		1148079	9716		100.000				100.000



(S)-3-cyclopropyl-1-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-one (**3j**)

The reaction mixture was stirred for 36 hours instead of 11 hours. Purified by silica gel chromatography (Hexane : DCM = 50 : 50 → 0 : 100, DCM : MeOH = 100 : 0 → 99.5 : 0.5) to obtain **3j** as a colorless liquid (66 mg, 70%, 87% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 2H), 7.53 (ddd, J = 6.6, 3.8, 1.2 Hz, 1H), 7.43 (dd, J = 10.3, 4.7 Hz, 2H), 3.16 (dd, J = 14.9, 6.9 Hz, 1H), 2.98 (dd, J = 14.9, 6.8 Hz, 1H), 1.61 – 1.48 (m, 1H), 1.06 – 0.93 (m, 2H), 0.78 – 0.66 (m, 1H), 0.43 – 0.28 (m, 2H), 0.20 – 0.11 (m, 1H), 0.01 (td, J = 9.1, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.62, 137.61, 132.61, 128.39, 128.29, 82.99, 46.29, 37.60, 24.94, 24.85, 18.60, 4.86, 4.27. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 33.25. HRMS (ESI) calculated for $[C_{19}H_{27}BO_3+H]^+$: 315.21260, found: 315.21356; 87% *ee* was measured by HPLC (CHIRALCEL OD-H, n-hexane : i-PrOH = 99.4 : 0.6, 0.2 mL/min, wavelength = 254 nm, 30 ºC); t_R = 36.04 min (major), t_R = 31.22 min (minor); $[\alpha]_D^{22}$ = -11.6 (c = 1.11, DCM).



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Date	28-Apr-20, 21:44:39

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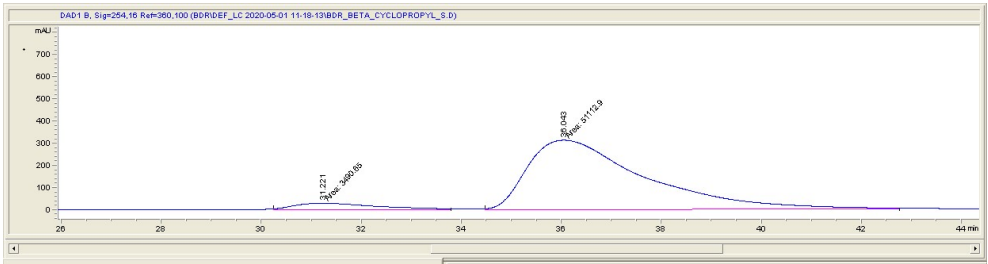

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File Path	C:\CHEM32\1\DATA\BDR\DEF_LC 2020-05-01 11-18-13\
Date	01-May-20, 12:21:03

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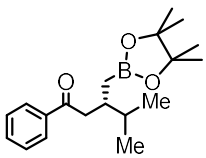
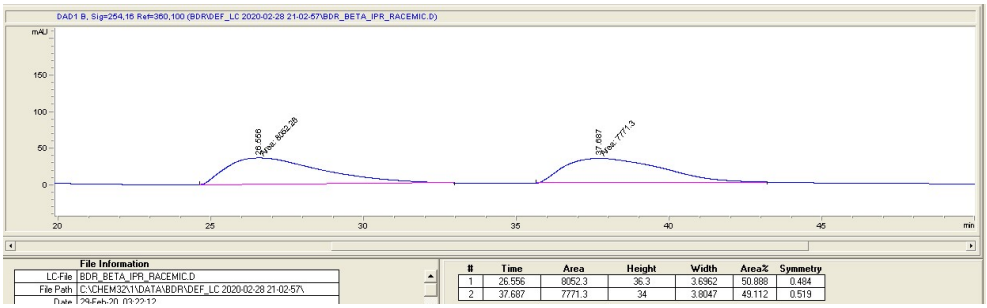
1	31.221	3490.7	29.4	1.9772	6.393	0.49
2	36.043	51112.9	313.3	2.7189	93.607	0.434



(S)-4-methyl-1-phenyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl) pentan-1-one (**3k**)

The reaction mixture was stirred for 36 hours instead of 11 hours. Purified by silica gel chromatography (Hexane : DCM = 50 : 50 → 0 : 100, DCM : MeOH = 100 : 0 → 99.5 : 0.5) to obtain **3k** as a yellowish liquid (64 mg, 68%, 87% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.98 (m, 2H), 7.53 (td, *J* = 7.0, 1.2 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 2.97 (dd, *J* = 15.6, 7.1 Hz, 1H), 2.86 (dd, *J* = 15.6, 6.5 Hz, 1H), 2.33 – 2.23 (m, 1H), 1.70 (dtd, *J* = 13.6, 6.8, 4.4 Hz, 1H), 1.21 (d, *J* = 3.0 Hz, 12H), 0.93 – 0.82 (m, 7H), 0.75 (dd, *J* = 15.7, 8.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.82, 137.50, 132.60, 128.37, 128.26, 82.94, 42.67, 36.60, 31.84, 24.85, 24.81, 19.69, 18.36. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B NMR (128 MHz, $CDCl_3$) δ 34.20.; HRMS (ESI) calculated for $[C_{24}H_{31}BO_3+H]^+$: 317.22825, found: 317.22921; 87% *ee* was measured by HPLC (CHIRALCEL OD-H, n-hexane : i-PrOH = 99.4 : 0.6, 0.2 mL/min, wavelength = 254 nm, 30 ^{o}C); t_R = 38.89 min (major), t_R = 30.02 min (minor); $[\alpha]_D^{22}$ = -10.6 (c = 1.06, DCM).



File Information

LC-File	BDR_BETA_IPR_RACEMIC.D
File Path	C:\CHEM32\1\DATA\BDR\DEF_LC 2020-02-28 21-02-57\
Date	29-Feb-20 03:22:12

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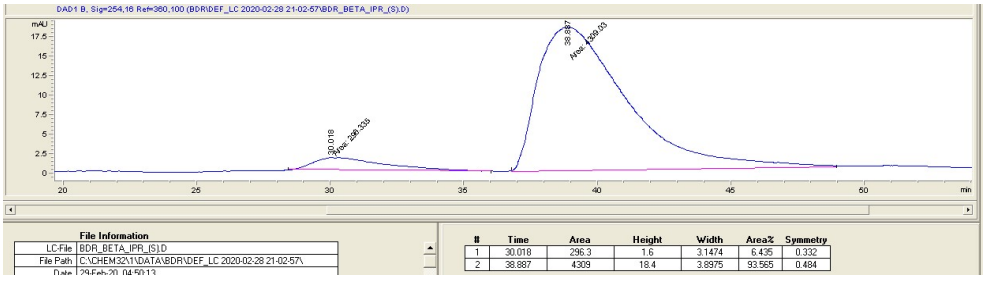

File Information

LC-File	BDR_BETA_IPR_(S).D
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Date	29-Feb-20 04:50:13

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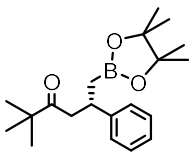
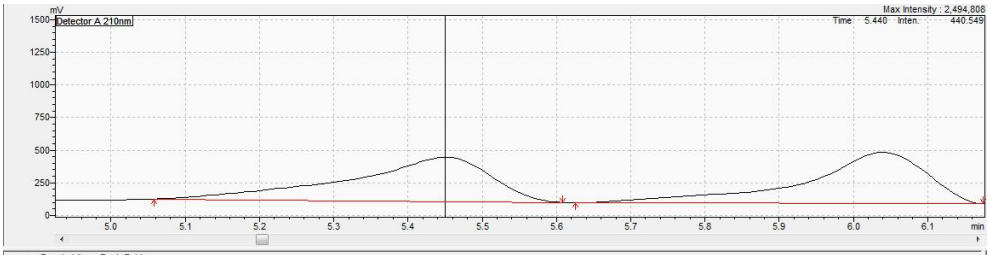
2	38.887	4309	18.4	3.8975	93.565	0.484



(S)-2,2-dimethyl-5-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-one (**3q**)

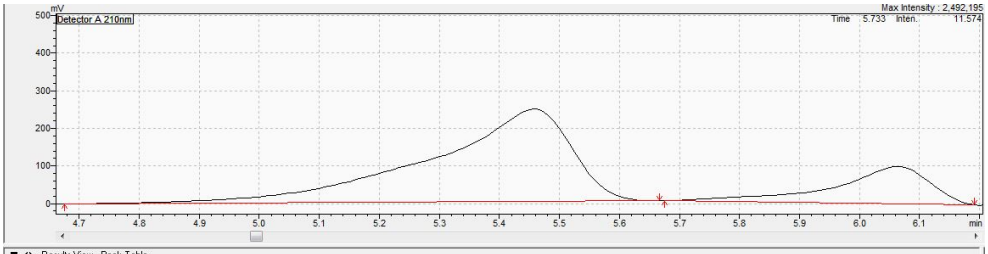
Purified by silica gel chromatography (Hexanes : DCM = 100 : 0 → 0 : 100) to obtain **3q** as a yellowish liquid (61 mg, 62%, 57% *ee*). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.23 (d, J = 4.3 Hz, 4H), 7.12 (dt, J = 8.6, 4.3 Hz, 1H), 3.47 (dq, J = 13.8, 6.9 Hz, 1H), 2.84 – 2.73 (m, 2H), 1.07 (d, J = 11.9 Hz, 12H), 1.01 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.16, 146.65, 128.06, 127.34, 125.91, 82.92, 82.79, 45.86, 44.00, 36.43, 26.02, 24.79, 24.67, 24.58. The carbon bound to the boron was not detected due to quadrupolar relaxation. ^{11}B (128 MHz, $CDCl_3$) δ 33.2; HRMS (ESI) calculated for $[C_{23}H_{29}BO_3+H]^+$: 365.2283, found: 365.2296; 57% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 °C); t_R = 5.46 min (major), t_R = 6.06 min (minor); $[\alpha]_D^{22}$ = -2.6 (c = 1.05, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	5.451	4445978	339277	M	50.111				50.111
2	6.040	4426303	392598	M	49.889				49.889
Total		8872281	731875		100.000				100.000

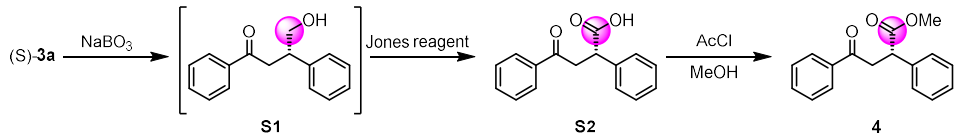


Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	5.457	3970967	245205	M	78.388				78.388
2	6.062	1094838	98984	M	21.612				21.612
Total		5065805	344189		100.000				100.000

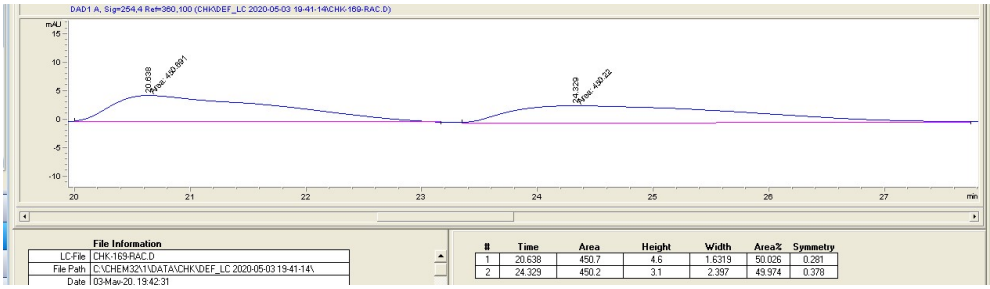
Experimental details on Scheme 2.1 (Further derivatizations).

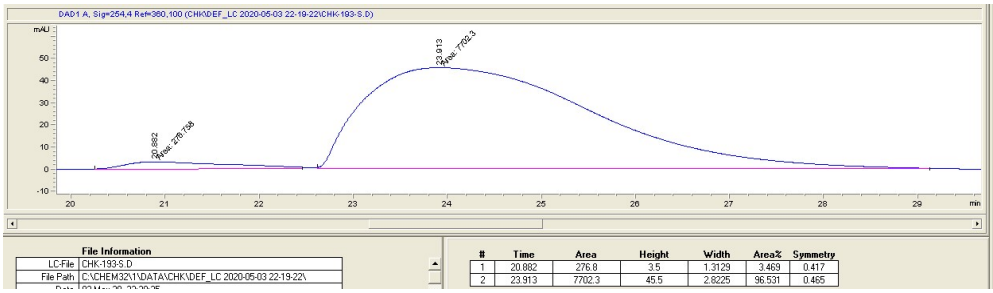


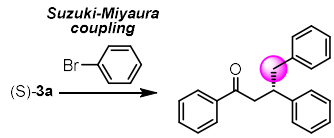
methyl (S)-4-oxo-2,4-diphenylbutanoate (**4**)

4 mL dram-vial was filled with (S)-**3a** (92%ee, 0.37 mmol, 100 mol%, 128 mg), $NaBO_3 \bullet 4H_2O$ (0.74 mmol, 200 mol%,114 mg). The reagents were dissolved in THF : MeOH = 1:1 (v/v) solution (1.6 mL). When the reaction was completed, the reaction mixture was extracted with EA/brine. The solvent of organic layer was changed into THF (0.8 mL). Then, 2.5M Jones reagent (CrO_3/H_2SO_4, 0.56 mmol, 150 mol%, 0.23 mL). After 3 hours, the reaction mixture was extracted with EA/$NH_4Cl_{(aq)}$. The organic layer, which was dried by Na_2SO_4, was concentrated *in vacuo* to get **S2**. Finally, AcCl (0.74 mmol, 200 mol%, 52 μL) and **S2** was dissolved in MeOH (1 mL). After 8 hours, the reaction mixture underwent extraction (EA/brine), followed by purification by flash column chromatography (Hexanes : EA = 100 : 0 → Hexanes : EA = 75 : 25 to obtain **4** (51 mg, 51%, 93% *ee*). *rac*-**4** was synthesized by using *rac*-**3a** via same reaction conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.93 (m, 2H), 7.56 (ddd, J = 6.8, 3.9, 1.2 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.39 – 7.29 (m, 5H), 4.31 (dd, J = 10.3, 4.1 Hz, 1H), 3.96 (dd, J = 18.0, 10.3 Hz, 1H), 3.70 (s, 3H), 3.28 (dd, J = 18.0, 4.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.58, 173.81, 138.31, 136.35, 133.28, 128.88, 128.56, 128.05, 127.79, 127.52, 52.31, 46.32, 42.77. 93% *ee* was measured by HPLC (CHIRALCEL OD-H, *n*-hexane : *i*-PrOH = 98.5 : 1.5 →

98:2, 0.8 mL/min, wavelength = 254 nm, 30 °C); t_R = 23.91 min (major), t_R = 20.88 min (minor); $[\alpha]_D^{22}$ = +84.4 (c = 0.73, DCM).



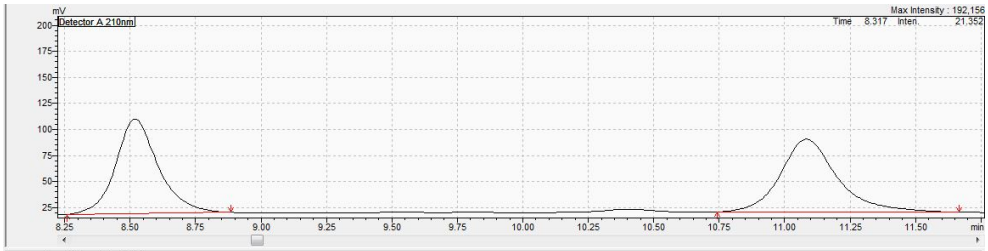




5

(S)-1,3,4-triphenylbutan-1-one (**5**)

In a nitrogen-filled glove box, 4 mL dram-vial was filled with (S)-**3a** (92%ee, 0.47 mmol, 100 mol%, 164 mg), $Pd_2(dba)_3$ (0.009 mmol, 2 mol%, 8.7 mg), Ruphos (0.019 mmol, 4 mol%, 8.8 mg), NaO*t*Bu (1.9 mmol, 400 mol%, 179 mg), and bromobenzene (0.71 mmol, 150 mol%, 73 μL) in toluene (1.6 mL) and H_2O (0.16 mL). The reaction mixture was stirred for 24 hours at 80°C. After cooling down, the reaction mixture was extracted with EA/Brine. The organic layer, which was dried by Na_2SO_4, was concentrated *in vacuo*. The concentrated crude mixture was purified by flash column chromatography chromatography (Hexanes : EA = 100 : 0 → Hexanes : EA = 97 : 3) to obtain **5** (95 mg, 72%, 91% *ee*). *rac*-**5** was synthesized by using *rac*-**3a** via same reaction conditions. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.31 – 7.17 (m, 8H), 7.11 (d, J = 7.3 Hz, 2H), 3.71 (p, J = 7.2 Hz, 1H), 3.35 (qd, J = 16.8, 7.0 Hz, 2H), 3.12 – 2.92 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.84, 144.09, 139.79, 137.16, 132.89, 129.25, 128.48, 128.33, 128.15, 127.96, 127.63, 126.37, 126.06, 44.12, 43.00, 42.97. 91% *ee* was measured by HPLC (CHIRALPAK IA, *n*-hexane : *i*-PrOH = 98.5 : 1.5 → 98:2, 1.0 mL/min, wavelength = 210 nm, 30 °C); t_R = 8.51 min (major), t_R = 11.04 min (minor); $[\alpha]_D^{22}$ = -31.1 (c = 0.83, DCM).



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

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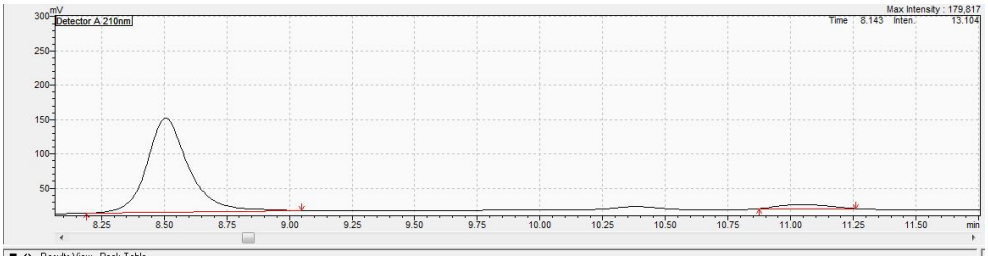
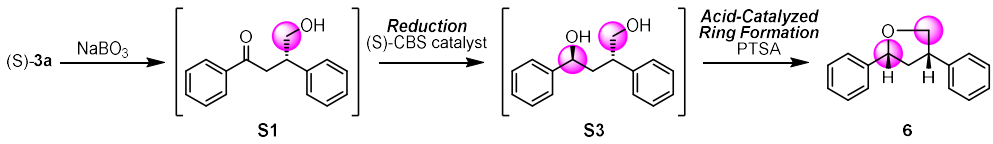
1	8.519	1026708	90898	M	49.239				49.239
2	11.083	1060514	70052	M	50.761				50.761
Total		2087223	160951		100.000				100.000



Results View - Peak Table

Peak Table | Compound | Group | Calibration Curve

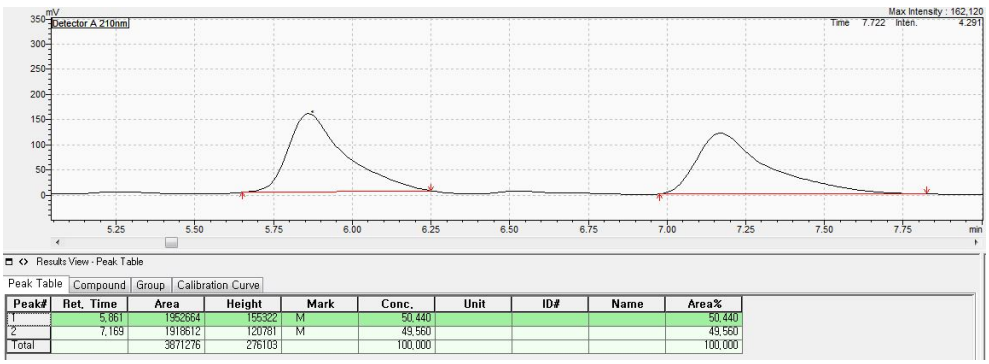
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	8.506	1590365	137116	M	95.214				95.214
2	11.040	79945	6067	M	4.786				4.786
Total		1670309	143183		100.000				100.000



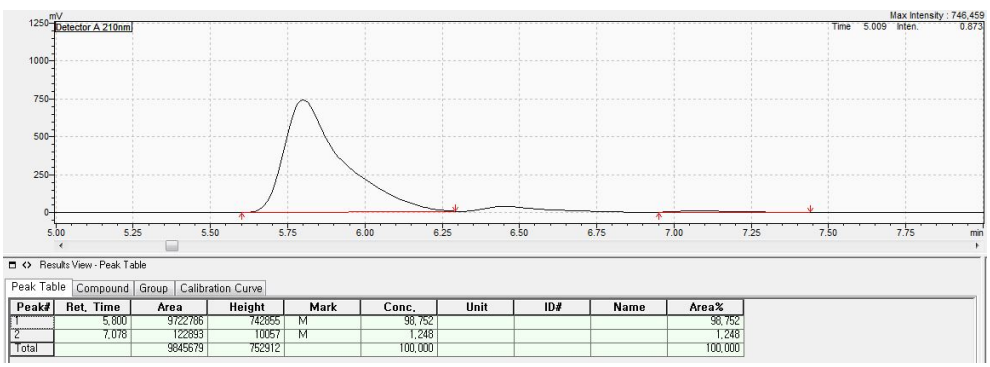
(2R,4S)-2,4-diphenyltetrahydrofuran (*ent*-Calyxolane B, **6**)

4 mL dram-vial was filled with (S)-**3a** (92%ee, 0.37 mmol, 100 mol%, 127 mg), $NaBO_3 \bullet 4H_2O$ (0.74 mmol, 200 mol%,114 mg). The reagents were dissolved in THF : MeOH = 1:1 (v/v) solution (1.6 mL). When the reaction was completed, the reaction mixture was extracted with EA/Brine. The organic layer, which was dried by Na_2SO_4, **S1** was roughly purified by silica filter with an eluent (*n*Hexane : EA = 7 : 3). After the filtrate was concentrated *in vacuo*, **S1** was dissolved in anhydrous THF (0.3 mL). The solution was injected into pre-activated (R)-CBS catalyst (0.08 mmol, 20 mol%, 22 mg) by 1M $BH_3 \bullet$THF (0.74 mmol, 200 mol%, 740 μL) in anhydrous THF (0.5 mL) at 0 ºC. After 8 hours, same work-up (extraction, silica filter, and concentration) was conducted to get **S3** with moderate purity. **S3** and PTSA (0.04 mmol, 10 mol%, 6.9 mg) was dissolved by 1,2-DCE (1 mL) and stirred for 12 hours at 40 ºC. The reaction mixture was extracted with EA/Brine. The organic layer, which was dried by Na_2SO_4, was concentrated *in vacuo*. The concentrated crude mixture was purified by flash column chromatography (Petroleum ether : EA = 100 : 0 → Petroleum ether : EA = 98 : 2) to obtain **6** (40 mg, 48%, 98% *ee*). *rac*-**6** was synthesized by using *rac*-**3a** via same reaction conditions; ketone reduction was conducted by $NaBH_4$ (0.6 mmol, 200 mol%, 23mg) instead of (R)-CBS catalyst and $BH_3 \bullet$THF. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.17 (m, 10H), 5.08 (dd, J = 10.2, 5.7 Hz, 1H), 4.37 (t, J = 8.3 Hz, 1H), 4.03 (t, J = 8.5 Hz, 1H), 3.75 – 3.58 (m, 1H), 2.77 (dt, J = 12.8, 6.6 Hz,

1H), 2.02 (dd, J = 22.2, 11.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.65, 141.70, 128.61, 128.43, 127.40, 127.25, 126.65, 125.71, 81.84, 75.11, 46.03, 43.73. 98% *ee* was measured by HPLC (CHIRALCEL OD, *n*-hexane : *i*-PrOH = 90 : 10, 1.0 mL/min, wavelength = 210 nm, 30 ºC); t_R = 5.80 min (major), t_R = 7.08 min (minor); $[\alpha]_D^{22}$ = +46.4 (c = 0.61, DCM).

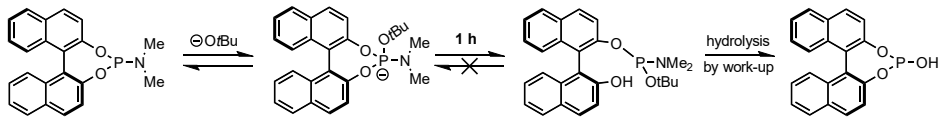


Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	5,861	1952664	155322	M	50,440				50,440
2	7,169	1918612	120781	M	49,560				49,560
Total		3871276	276103		100,000				100,000



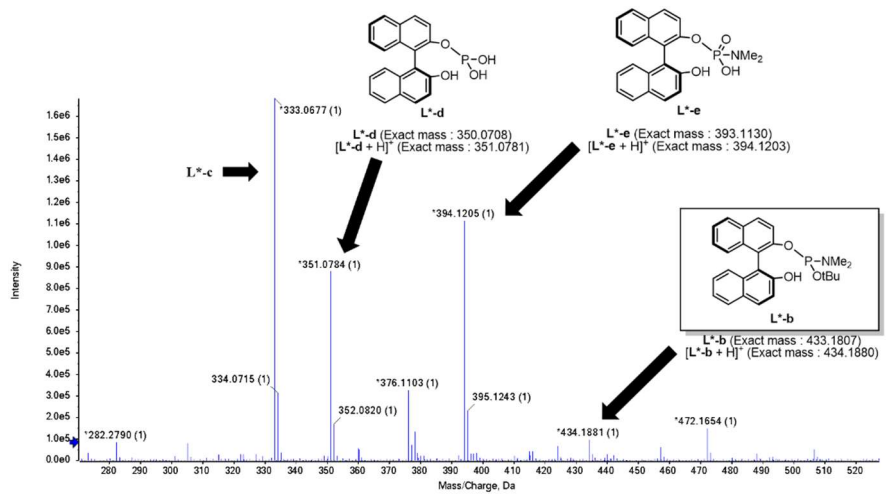
Peak#	Ret. Time	Area	Height	Mark	Conc.	Unit	ID#	Name	Area%
1	5,800	9722786	742855	M	98,752				98,752
2	7,078	122893	10057	M	1,248				1,248
Total		9845679	752912		100,000				100,000

HRMS Data on Additive Effect Studies

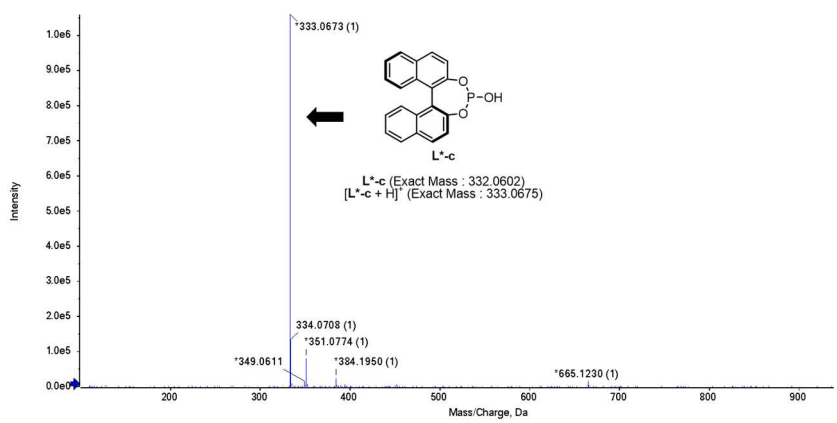


L* (^{31}P) δ:150 ppm | **L*-a** | **L*-b** (^{31}P) δ:140 ppm | **L*-c** (^{31}P) δ:155 ppm

(a) **L*-b**[a] (ESI-HRMS)



(b) **L*-c**[b] (ESI-HRMS)



[a]HRMS analysis was conducted after the solution in Conditions C (**Figure 2.2**) had been filtered via syringe filter. [b]**L*-c** could be obtained in reasonable purity by leaving the solution in Conditions D in the air over 12 hours.

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국문 초록

본문에서는 구리 촉매를 이용한 1,1-비스피나콜라토보릴메테인의 입체 선택적인 1,4-첨가반응을 소개한다. 이 반응은 알파, 베타-불포화 케톤 (찰콘 및 그의 유도체)에 대해 입체선택적으로 보릴-알킬족을 첨가한다. 생성물인 감마-보릴다이하이드로찰콘은 여러 방법으로 작용기를 선택적으로 변화시킬 수 있다. 이 반응을 개발하는 과정에서, 리튬-아세틸아세토네이트의 효과를 31P 및 11B NMR 분석법을 사용하여 밝혀내었다.

주요어: 알파, 베타-불포화 케톤, 입체 선택적, 감마-보릴다이하이드로찰콘, 1,1-비스피나콜라토보릴메테인

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